# Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF Review of TA559)

For public – AIC and CIC redacted

**Technology appraisal committee C [06 September 2022]**

**Chair:** Richard Nicholas

**Lead team:** Natalie Hallas, Alex Cale, Ugochi Nwulu

**Evidence assessment group:** Kleijnen Systematic Reviews

**Technical team:** Lewis Ralph, Vicky Kelly, Ross Dent

**Company:** Kite, a Gilead Company

NICE

# Background on NHL, DLBCL and PMBCL

## Fast growing lymphomas affecting approximately 5,500 people

### Epidemiology

- NHL comprises blood cancers originating primarily in B-cells; DLBCL most common
- Around 14,200 people diagnosed with NHL each year in the UK
- Each year about 5,500 people are diagnosed with DLBCL; around 40% of NHL
- PMBCL makes up around 5% of all NHL cases

### Diagnosis and classification

- NHL diagnosed with biopsy of lymph node to test type, grade, immunohistochemistry and cytogenetics
- DLBCL and PMBCL are high grade (fast growing) lymphomas

### Symptoms and prognosis

- Fatigue, night sweats, and painful swelling/lumps in the neck, armpit and groin
- Relapsed/refractory outcomes with standard of care are poor – low levels of response and limited survival
- High burden of disease associated with NHL affects people's quality of life



**Abbreviations:** DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma

# Axicabtagene ciloleucel (Yescarta, Gilead)

| | |
|---|---|
| **Marketing authorisation** | • Marketing authorisation granted by EMA August 2018:<br>'for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy' |
| **Mechanism of action** | • CAR T-cell therapy that uses autologous T-cells engineered to express receptors directed against the tumour antigen CD19 |
| **Administration** | • T cells harvested and genetically modified to express a CAR<br>• Each single infusion bag contains anti-CD19 CAR-T cells in approximately 68 ml for a target dose of 2 x 106 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 106 – 2 x 106 cells/kg), max 2 x 108 anti-CD19 CAR T cells |
| **Price** | • £280,451 per 68 ml single infusion bag<br>• Approved commercial arrangement (commercial in confidence) |



**Abbreviations:** CAR, chimeric antigen receptor; CD19, cluster of differentiation 19; EMA, European Medicines Agency; kg, kilogram; ml, millilitre.

# Patient perspectives

## Chemotherapy takes significant toll on people with DLBCL and PMBCL

**Submissions from Anthony Nolan and Blood Cancer UK**

- Multiple prior lines of therapy are attempted with limited or no success before CAR-T is an option for people
- Long courses of harsh chemotherapy treatments take a significant physical and mental toll on people with DLBCL or PMBCL
- DLBCL and PMLBCL have a significant effect on day-to-day life, it takes over people and carers' lives and can feel like a full-time job
- Large mental health impact, people 'downhill, mentally for a prolonged period' despite support from friends and family
- Carers feel isolated, lonely, anxious and helpless when caring for someone with DLBCL or PMLBCL
- "CAR-T was quicker, less harsh on my body….. The most important advantage above all is the success of the treatment. Chemo failed for me and I was told other types would likely have a similar response. However CAR-T worked and continues to work"

*I felt so weak after chemotherapy that I really didn't know how my body or my mind was going to cope with everything that was to come*

*Caring takes over every aspect of your life. It significantly impacted our quality of life, and that of my son*

**Abbreviations:** CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma

# Clinical perspectives
## Innovative potentially curative treatment that meets unmet need

**Submissions from clinical experts**

- Expected to provide clinical benefits for younger patients relapsing after autologous stem cell transplant or who have refractory disease
- CAR-T provides durable remissions (and probable cures) in a minority of patients; for people who receive cells ~40% have this response.
- Some patients will not make it to infusion so proportion likely less in whole third-line population
- CAR-T administration requires specialist centres
- CAR-T therapy is highly innovative and meets the unmet need of providing a potentially curative treatment option
- Real-world CAR-T evidence has largely mirrored clinical trial evidence
- Little further comparative data has been generated in the last 2-3 years


**Abbreviations:** CAR, chimeric antigen receptor.

# Recap: Summary of original appraisal (TA559) and CDF Review

1st committee meeting (July 2018) → 2nd committee meeting (Sept 2018) → Guidance published and CDF entry (Nov 2018) → CDF Data collection ends (Feb 2022) → CDF Review (ID3980) ACM1 (Sept 2022)

**TA559 Recommendation:** Axicabtagene ciloleucel therapy is recommended for use within the CDF as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies, only if the conditions in the managed access agreement are followed

Although significant uncertainty in cost-effectiveness estimates, committee concluded many assumptions in the company's base case were plausible and might be verified through further data collection.

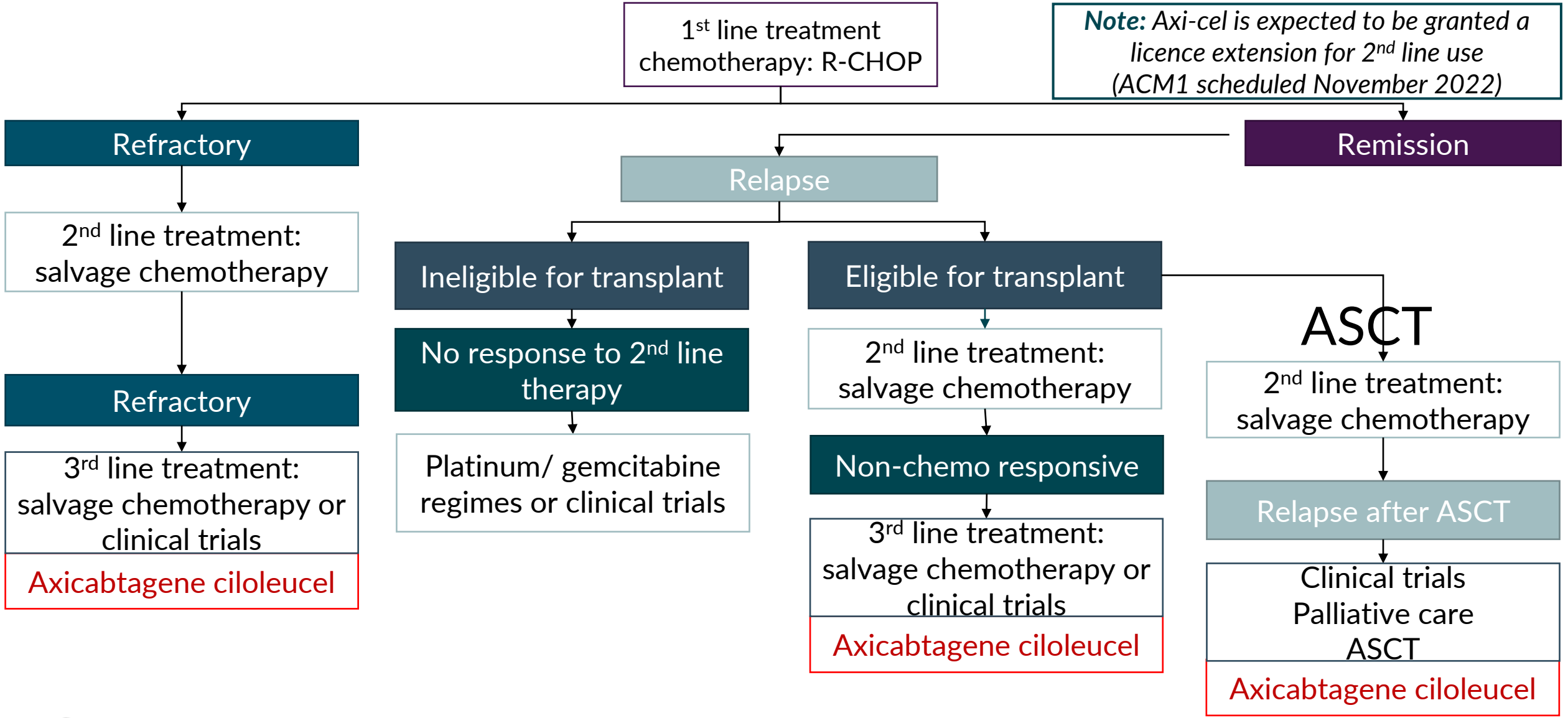
To address uncertainties, further data was to be collected:

- ZUMA-1 clinical trial data
  - OS, PFS and intravenous immunoglobin G (IVIG) use
- SACT data
  - OS and IVIG use

**Abbreviations:** ACM, appraisal committee meeting; CDF, Cancer Drugs Fund; OS, overall survival; progression-free survival; SACT, systemic anti-cancer therapy; TA, technology appraisal.

# Recap: Treatment pathway

## Axicabtagene ciloleucel could be used in 3 possible positions




**Abbreviations:** ASCT, allogenic stem cell transplant; R-CHOP, rituximab – cyclophosphamide, hydroxydaunomycin, oncovin, prednisolone.

# Recap: Key uncertainties in TA559

| Uncertainties in TA559 | | Committee considerations |
|---|---|---|
| **Convergence of PFS and OS curves** | • Company assumed difference between survival plateaus for axi-cel OS and PFS maintained<br>• ERG provided 2 analyses where OS and PFS converge; no curative post-progression assumptions<br>• No evidence OS and PFS converging in ZUMA-1; data immature | • Acknowledged future ZUMA-1 data-cuts planned - these may provide more certainty<br>• Heard from the company that PFS and OS had not converged in the trial data |
| **Use of IVIG** | • ZUMA-1 showed small number needed IVIG<br>• NHSE explained B-cell aplasia is a likely consequence of successful axi-cel treatment<br>• IVIG use after axi-cel remained an unknown | • Concerned company underestimated IVIG<br>• Need for IVIG treatment remained unknown, so effect of B-cell aplasia mortality risk uncertain |
| **OS from the infusion of axi-cel** | • Median OS not reached; data immaturity led to uncertainty in long-term estimates<br>• Company applied mixture cure model with 50% cure fraction<br>• ERG used a hybrid approach | • Company mixture cure model likely to overestimate cure fraction<br>• ERG hybrid approach could be conservative<br>• Concluded OS gain likely to be somewhere in-between |

**Abbreviations:** Axi-cel, axicabtagene ciloleucel; CDF, Cancer Drugs Fund; ERG, evidence review group; IVIG, intravenous immunoglobin; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

# Outstanding issues following technical engagement

## PFS only outstanding impactful issue

| | Issue | Resolved? | ICER impact |
|---|---|---|---|
| 1 | Additional comparator data available during the managed access period | Partially | Unknown |
| 2 | Modelling long-term salvage therapy overall survival | Partially | Unknown |
| 3 | Long-term plateau in progression-free survival | No | Large |
| 4 | IVIG use in the model<br>*Following TE, SACT data used to inform IVIG in company and ERG base case* | Yes | Small |

**Abbreviations:** ERG, evidence review group; IVIG, intravenous immunoglobin; PFS, progression-free survival; SACT, systemic anti-cancer therapy; TE, technical engagement.

# Clinical effectiveness

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# Key clinical trials

## ZUMA-1 overall survival data matured to 60 months

| | ZUMA-1 | SCHOLAR-1 | SACT data set |
|---|---|---|---|
| **Design** | Phase 1/2, single-arm, multi-centre, open-label study | Patient level historical control study | Observational study |
| **Population** | Adults with aggressive B-cell NHL (DLBCL, PMBCL, and TFL) that was either refractory to treatment or had relapsed ≤ 12 months after ASCT | Adults with relapsed/refractory DLBCL and PMBCL | Adults with relapsed/refractory DLBCL and PMBCL, after 2+ lines of systemic therapy, and TFL after 1+ lines of systemic therapy |
| **Intervention** | Axicabtagene ciloleucel | Salvage chemotherapy, rituximab maintenance, observation post-ASCT | Axicabtagene ciloleucel |
| **Comparator(s)** | Not applicable | Not applicable | Not applicable |
| **Duration** | 60 months minimum follow-up | Approx. 4 years median follow-up | Unclear |
| **Outcomes** | • OS<br>• PFS<br>• IVIG usage | • OS<br>• Objective response rate | • OS<br>• IVIG usage |
| **Locations** | 24 centres (23 USA, 1 Israel) | USA, Canada, France | UK |
| **Used in model?** | Yes | Yes, comparator arm | No |

**Abbreviations:** Approx., approximately; ASCT, allogenic stem cell transplant; DLBCL, diffuse large B-cell lymphoma; IVIG, intravenous immunoglobin; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; SACT, systemic anti-cancer therapy; TFL, transformed follicular lymphoma; UK, United Kingdom; USA, United States of America.

# ZUMA-1 efficacy data update (1)

## OS updated to 60 months, PFS to 24 months

**Update from TA559**

- TA559 used August 2017 data cut (median follow-up 15.4 months, median OS not reached, median PFS 5.8 months)
- Key uncertainties were OS estimates for axi-cel and convergence of OS and PFS
  - OS and PFS were to be updated during the data collection period with the latest ZUMA-1 data to address uncertainty
- Latest ZUMA-1 data cut (11 Aug 2021) includes 60 months minimum follow-up
- PFS only updated up to a follow-up of 24 months, due to protocol mandate

**Key 60-month OS results**

- Median follow-up: [redacted] months; Max: [redacted] months
- Median survival: [redacted] months
- [redacted] patients ([redacted]%) had died at database lock
- 60-month survival rate in people with complete response: Phase I, [redacted]%; Phase II, [redacted]%

**Key 24-month PFS results**

- Median follow-up: [redacted] months
- Median PFS: [redacted] months
- Observed plateau at [redacted] months ~40%

NICE **Abbreviations:** KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

# ZUMA-1 efficacy data update (2)

## OS and PFS plateau before heavy censoring

**ZUMA-1 OS Kaplan–Meier (60 months; Aug 21 DBL)**

OS plateau at ~[redacted]% – heavy censoring at [redacted] months

**ZUMA-1 PFS Kaplan–Meier (24 months; Aug 21 DBL)**

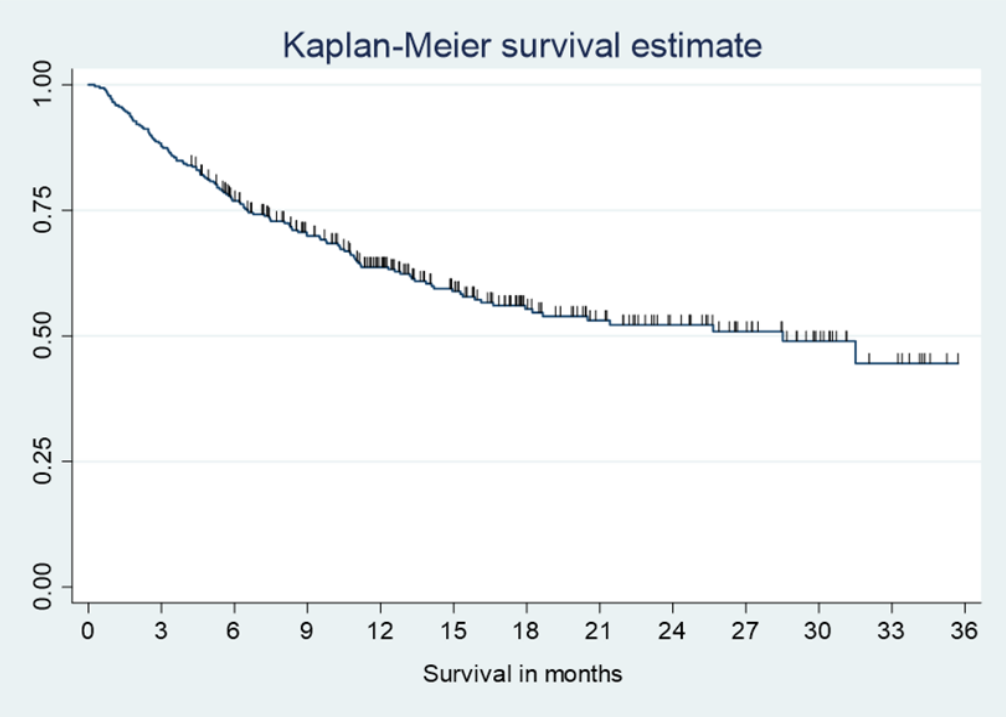
PFS plateau at ~[redacted]% – heavy censoring at [redacted] months

NICE **Abbreviations:** Aug, August; DBL, database lock; OS, overall survival; PFS, progression-free survival.

# Systemic anti-cancer therapy efficacy
## SACT overall survival appears consistent with ZUMA-1

- Real-world axi-cel effectiveness data in the CDF population (between Dec 2018 and Oct 2021)
- Median age receiving axi-cel infusion, 59.5 years (ZUMA-1, 58 years)
- Median OS, 28.5 months (ZUMA-1, 23.5 months)
- 37% of people had missing ECOG performance status (0 = 24%; 1 = 35%; 2 = 4%)

**SACT OS Kaplan–Meier (Oct 21)**




**SACT versus ZUMA-1 OS**

| Month | ZUMA-1 | SACT |
|---|---|---|
| 6 | [redacted] | 77% |
| 12 | [redacted] | 64% |
| 18 | [redacted] | 55% |
| 24 | [redacted] | 52% |
| 30 | [redacted] | 49% |
| 36 | [redacted] | 45% |

**Key:** SACT, Systemic Anti-Cancer Therapy.
**Notes:** Comparison made with ZUMA-1 Phase I and II mITT (N = 108, 11 Aug 21 DBL)

**Abbreviations:** CDF, Cancer Drugs Fund; DBL, database lock; Dec, December; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; mITT, modified intention to treat; Oct, October; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

# Salvage chemotherapy – SCHOLAR-1

- Company modelling approach unchanged since TA559
- Company adjusted SCHOLAR-1 to ensure comparability with the ZUMA-1 population
    - Unknown and ECOG-PS 2 to 4 excluded, consistent with ERG-preferred approach
    - Primary refractory patients excluded, consistent with the marketing authorisation
    - Resulting OS curve was adjusted to reflect outcomes for a population in which 10% of patients have subsequent SCT, consistent with TA567 (tisagenlecleucel for DLBCL)
- Committee preferred generalised gamma to extrapolate OS for salvage chemotherapy in TA559

**KM and selected parametric curves (generalised gamma) for the non-SCT and SCT populations**

[redacted]

**OS and PFS extrapolations for axi-cel and salvage chemotherapy**

[redacted]

**Abbreviations:** DLBCL, diffuse large B-cell lymphoma; ECOG-PS, Eastern Cooperative Oncology Group performance score; ERG, evidence review group; OS, overall survival; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant; TA, technology appraisal.

# Key issues 1&2: Comparator data - modelling long term OS (1)

## No new data, comparator still informed by SCHOLAR-1

**SCHOLAR-1 extrapolation and Radford et al. 2019**

### Background

- Results from SCHOLAR-1 used to model long-term OS for the salvage chemotherapy arm in TA559
- CDF Terms of Engagement states that in addition to using SCHOLAR-1 data, the submission should use "*any additional data that has become available during the period of managed access to inform the comparator arm*"

### Company

- Conducted a targeted literature review of chemotherapy in 3L DLBCL, only one study based in the UK (Radford et al. 2019)
- Company extrapolation using SCHOLAR-1 data broadly consistent with the 3L data from Radford et al. 2019
- Argue SCHOLAR-1 still most appropriate source for long-term OS outcomes for the comparator

**Abbreviations:** 3L, third-line; DLBCL, diffuse large B-cell lymphoma; ERG, evidence review group; OS, overall survival; TA, technology appraisal;

# Key issues 1&2: Comparator data - modelling long term OS (2)

## No new data, comparator still informed by SCHOLAR-1

**ERG and NICE technical team comments**

- Indirect comparison of axi-cel and salvage chemotherapy is made without any measures of uncertainty; interpretation difficult
- The company targeted literature review found 3 sources, with only 1 in the UK; Search only used 1 database, so important sources may have been missed
- Company excluded alternative comparator data as weren't conducted in the UK, but SCHOLAR-1 and ZUMA-1 not UK
- Company adjusted SCHOLAR-1 dataset to be more reflective of ZUMA-1 and UK practice; substantially reducing sample size from 562 to 133
  - Other studies not included by company: Radford (UK), N = 89; Fuiji (Japan), N = 189; Nakaya (Japan), N = 131
- Alternative OS scenarios explored by ERG indicate that results sensitive to changes in comparator OS extrapolation

**SCHOLAR-1 extrapolation and Radford et al. 2019**

Is SCHOLAR-1 the most appropriate data source for the comparator?

**Abbreviations:** 3L, third-line; DLBCL, diffuse large B-cell lymphoma; ERG, evidence review group; OS, overall survival; TA, technology appraisal;

# Cost effectiveness

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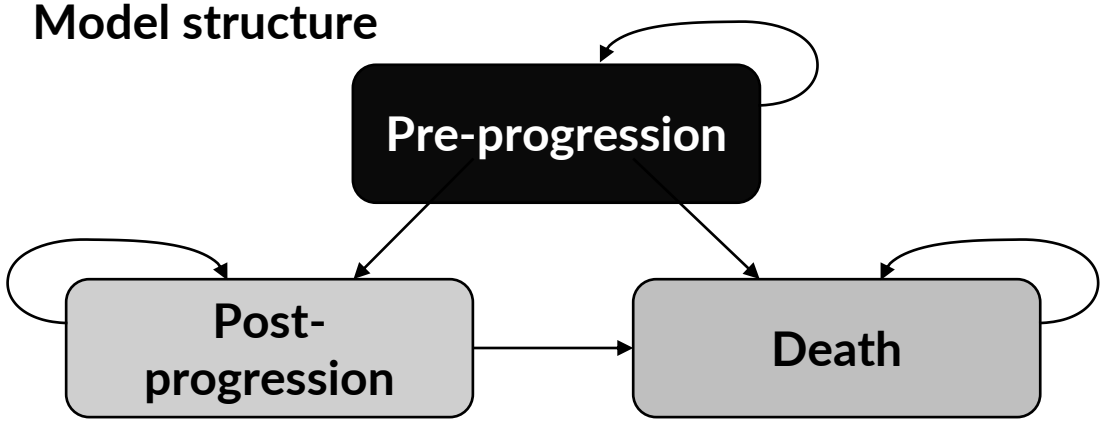
# Company's cost-effectiveness model overview

## 3-state partitioned survival model – OS and PFS modelled independently

### Key model parameters

| Parameter | Assumption and data source |
|---|---|
| Time horizon; Cycle length | 44 years; 1 month |
| Discount rate | 3.5% |
| Overall survival | **Axi-cel:** log-logistic MCM<br>**BSC:** standard generalized gamma, ZUMA-1 60 month data |
| Progression-free survival | **Axi-cel:** standard Gompertz<br>**BSC:** OS/PFS ratio, ZUMA-1 24 month data |
| Utility | Health state utility, ZUMA-1 safety population |
| IVIG | SACT: 16% of people every 4 weeks for 6.5 months |

### Model structure




[redacted]

**Abbreviations:** BSC, best supportive care; IVIG, intravenous immunoglobin; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival.

# Axi-cel overall survival predictions

## Updated OS with ZUMA-1 60-month data, mixture cure models used

### Background

- Standard models implausible; MCMs used in TA559 base case
- NICE DSU TSD 21 released after TA559 supports flexible models
- ToE: Use latest ZUMA-1 data to inform OS; SACT to validate

### Company

- MCMs used to combine:
  - Estimated long-term survivor ("cure") fraction
  - Age-/gender-matched mortality for long-term survivors
  - Parametric model for non-long-term survivors
- All MCMs provided a good fit to the data, plausible cure fractions and long-term estimates
- Log-logistic selected in base case (best statistical fit)

### ERG comments

- Updated data cut reduced uncertainty of cure fraction and was lower than the 50% fraction in TA559
- Agreed with company approach; highlighted all MCM and spline curves higher than KM – may overestimate survival

**ZUMA-1 MCM OS extrapolations**

**Table x** ZUMA-1 OS cure fractions

| Model | Implied cure fraction |
|---|---|
| Exponential | [redacted] |
| Weibull | [redacted] |
| Gompertz | [redacted] |
| Log-logistic [selected] | [redacted] |
| Log-normal | [redacted] |
| Generalised gamma | [redacted] |

**Abbreviations:** DSU, decision support unit; KM, Kaplan–Meier; MCM, mixture cure model; OS, overall survival SACT, systemic anti-cancer treatment; TA, technology appraisal; ToE, terms of engagement; TSD, technical support document.

# Key issue 3: Axi-cel progression-free survival (1)

## PFS only updated to 24 months, outcomes still uncertain

### Background

- TA559: standard Gompertz model, 12 months of data used before heavy censoring
- ToE: PFS to be updated with latest data to address uncertainty and convergence of PFS and OS curves

### Company

- Update: standard Gompertz, 24 months of data – to maintain consistency with TA559
- No protocol mandate to collect progression data after 24 months, any ZUMA-1 data after not consistent
- Argue that, as model uses mature "stable" survival data, further PFS will not likely change cost effectiveness
- State long-term ZUMA-1 data show few progression events between 2 and 4+ years; no evidence provided
- Following TE, extra scenario considers an SMR of 1.09 applied to PFS after 24 months, minimal ICER effect

### ERG and NICE technical team comments

- Requested PFS data beyond 24 months (e.g. 60-month data) to be provided; company did not provide
- Substantial censoring at Month 23/24 shows any plateau in PFS still uncertain
- Month 24-48: [redacted] OS events (with no censoring), possibly feature in PFS curve and would drop curve
- MCMs appropriate, allowing consistent modelling between OS and PFS
- Company SMR scenario still has assumption of long-term plateau in ZUMA-1 data at 2 years; other methods may not have minimal effect
- ERG next best standard model increases ICER by ~£17,000; ERG also ran MCM and spline scenarios



**Abbreviations:** OS, overall survival; PFS, progression-free survival; TA, technology appraisal; ToE, terms of engagement

# Key Issue: Axi-cel progression-free survival (2)

## PFS extrapolations remain uncertain

**ZUMA-1 PFS extrapolations: Standard parametric**

[redacted]

**ZUMA-1 PFS extrapolations: A, mixture cure; B, splines**

[redacted]

Company use KM to 35m to validate and inform Gompertz curve selection; despite heavy censoring at 23/24 months, <6% patients "at risk" 24-35m
Potentially misleading after month 24 – 'artificial plateau' created until Month 35 (no events but patients not followed up)

- Has missing PFS been appropriately accounted for?
- Which is the most appropriate extrapolation for PFS?

**Abbreviations:** evidence review group; m, month; KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival.

# Summary of company and ERG scenarios

## Consistent company and ERG base case following TE, different scenarios

**Assumptions in company and ERG base case**

| | Base case assumptions | Company scenarios | ERG scenarios |
|---|---|---|---|
| OS | Axi-cel: Log-logistic MCM<br>BSC: Generalised gamma | Axi-cel: 2-knots normal spline | BSC: Gompertz |
| | | | BSC: Log-logistic |
| | | | BSC: Log-normal |
| PFS | Axi-cel: Gompertz<br>BSC: OS/PFS ratio applied | SMR 1.09 applied to hazard of death at 24 months | Generalised gamma |
| | | | 2-knots normal spline |
| IVIG | 16% of people every 4 weeks and treatment duration 6.5 months | 16% of people **every 8 weeks** for 6.5 months | Updated SACT analysis<br>**19%** of people every 4 weeks for **9.5 months** |

Results containing confidential prices for other treatments will be presented in Part 2

**Abbreviations:** BSC, best supportive care; CMU, commercial medicines unit; ERG, evidence review group; IVIG, intravenous immunoglobin; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; SMR, standardised mortality ratio; TE, technical engagement.

# Base case results – includes axi-cel PAS

## *ERG and company base case aligns*

Deterministic incremental base case results – following technical engagement

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | | | |
| Axi-cel | [redacted] | [redacted] | [redacted] | [redacted] | £50,480 |

Probabilistic incremental base case results [run by ERG*]

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | | | |
| Axi-cel | [redacted] | [redacted] | [redacted] | [redacted] | £51,203 |

*The ERG identified (and corrected) an error in the company's model regarding the probabilistic sensitivity analysis (PSA)

Results containing confidential prices for other treatments will be presented in Part 2

**Abbreviations:** Axi-cel, axicabtagene ciloleucel; BSC, best supportive care; ERG: Evidence review group, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

# ERG deterministic scenario analysis – includes axi-cel PAS

**ERG scenario analyses (deterministic)**

| | Scenario (applied to company base case) | ICER (£) versus BSC |
|---|---|---|
| | Base case | £50,480 |
| **OS** | Gompertz used for BSC | £55,787 |
| | Log-logistic used for BSC | £46,048 |
| | Log-normal used for BSC | £46,977 |
| **PFS** | Generalised gamma for axi-cel | £67,765 |
| | Lognormal mixture cure model for axi-cel | £51,096 |
| | Spline model: two knots normal for axi-cel | £55,257 |
| **IVIG** | Updated SACT analysis (19% every 4 weeks for 9.5 months) | £50,815 |

Results containing confidential prices for other treatments will be presented in Part 2

**Abbreviations:** Axi-cel, axicabtagene ciloleucel; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin G; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; SMR, standardised mortality ratio.

# Other considerations

## Axi-cel innovative and meets end of life criteria

### Equality considerations

*Anthony Nolan*

- Tertiary oncology centres often difficult and expensive for patients to access on a regular basis

*NHSE*

- Noted in TA559 the need for a phased implementation period due to novelty of CAR-T treatments

### Innovation

- Single infusion and single treatment rather than recurrent cycles of traditional chemotherapy
- CAR-T treatments represented a step-change in management of people with R/R disease

### End of Life Criteria

- Met both short life expectancy and extension to life criteria in TA559



**Abbreviations:** CAR-T, chimeric antigen receptors cell therapy; R/R, relapsed/refractory; TA, technology appraisal.

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# Thank you.